REMARKS

Claim 36 is amended. Claims 36-41 are pending. The amendment of the existing claims does not affect inventorship. Support for the amendments is found in the specification as filed, see, e.g., Examples 1 and 2.

Claim Rejections – 35 USC § 112, second paragraph

Claims 36-41 are rejected under 35 USC § 112, second paragraph as being unclear. Specifically, "It is not clear what are 'variable amino acids' as this term is not defined in the specification (specification is using term 'variable positions' instead)." Claim 36 has been amended to correct a typographical error. The term intended was "variant amino acids," which has antecedent basis in step D) (i).

Applicants believe that claim 36, as amended, meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request this rejection be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph

Claims 36-41 are rejected under 35 USC § 112, first paragraph for the term 'variable amino acids' not being described in the specification. Claim 36 has been amended to correct a typographical error. The term intended was "variant amino acids," which has antecedent basis in step D) (i).

Applicants believe that claim 36, as amended, meets the requirements of 35 U.S.C. § 112, first paragraph. Applicants respectfully request this rejection be withdrawn.

Claim Rejections – 35 USC § 103

Claims 36-41 are rejected under 35 USC § 103 as being unpatentable over Wang et al (Protein Engineering, 9 (6), 479-484, 1996) and Dahiyat, 1997 (J. Mol. Biol., 1997, 273, 789-796).

As amended, all pending claims require the generation of a secondary library by using several specific steps. The secondary library is generated by combing an amino acid residue in the set of amino acid residues at each of the variable residue positions. The set of amino acid residues at each of the variable residue positions is generated by both selecting at least one variable amino acid at the relevant variable position from variant protein sequences in the primary library and selecting the amino acid residue of the target protein for the relevant variable position. All claims also require that the primary library be generated by "applying a force field

calculation to said plurality of variable residue positions and said coordinates." Additionally, at least one member of the secondary library must have a plurality of variant amino acids relative to the target protein.

The Office Action states:

> Fig 1 in Wang compiles sequences obtained by generating sets of residues for each "variable residue" in the order of energy efficiency and recombining them into sequences in the order of sequence of the original protein. Even though Wang does not teach directly which of the proteins is to be generated, it states that "the predicted mutant profile can act as a guide for protein engineering." (p. 483, last paragraph). Thus, it would be obvious to combine the residues indicated by force field calculations as being suitable and being low energy and using permutations of such "optimal" residues", to generate a library of optimized sequences (i.e., a "secondary" library).

> Since for each position Fig. 1 comprises both the substituted residues (ie., residues from "primary library") and the native residue, it results in a set as per step d), and a library as per step e). Since the latter library is comprised of sequences comprises native residues in addition to mutant residues in "primary" library, it is different in at least one member from the library comprised only of mutant residues.

Applicants respectfully disagree with the characterization of Wang. Figure 1 of Wang is the "mutant profile for calmodulin (PDB code 3cln). Substitutions are listed for each position along the sequence in descending order of energy. Residues in the lowest row are lowest in energy, while residues in the highest row are highest in energy." In other words, Wang teaches an analysis of the energies of each of the 20 types of amino acids when placed individually at every position of calmodulin. Figure 1 is not a primary library of variant sequences. Wang's statement that the mutant profile analysis "can act as a guide for protein engineering" is an invitation to experiment further. If a person of ordinary skill made the sequence of Row 1 of Figure 1, only 37 wild-type residues would remain out of 143 residues in calmodulin. Give that Row 1 mutates 74% of the residues in calmodulin, and each of these mutations is made independent of other mutations, it is highly unlikely that the sequence of Row 1 would be an active or stable molecule. Figure 1 cannot be fairly characterized as a primary library of variant proteins generated by "applying a force field calculation to said plurality of variable residue positions and said coordinates to generate a primary library comprising optimized variant protein sequences" as required by the amended claims. Figure 1 only shows the results when Wang applied a force field calculation to one residue at a time. Wang does not teach or suggest applying a force field calculation to multiple substitutions at once. At best, Wang's statement that one can use a mutant profile analysis to guide protein

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engineering is an invitation to generate a <u>primary</u> library, and even then it would not be a primary library generated in the method required by the pending claims.

Applicants respectfully submit that Wang does not teach or suggest the generation of a secondary library by any means. Further, Wang does not teach or suggest the generation of a secondary library wherein at least one member of the secondary library has a plurality of variant amino acids relative to the target protein. Neither does Dahiyat 1997 teach or suggest these limitations. Applicants respectfully submit that Wang does not teach or suggest steps C), D) or E) as required in claim 36.

Since Wang and Dahiyat 1997 not teach or suggest every limitation found in the amended claims, Applicants respectfully submit that these references do not make the pending claims obvious. Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Xencor, Inc.

Dated: September 22, 2008   By: / Kenton Abel /
                                                              Kenton Abel, Reg. No. 49,051
Customer No.: 33315
111 W. Lemon Ave.
Monrovia, CA 91016
Telephone: (626) 737-8089
Facsimile: (626) 256-3760